Spatiotemporal mosaic self-patterning of pluripotent stem cells using CRISPR interference.

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Public Summary:
Morphogenesis involves interactions of asymmetric cell populations to form complex multicellular patterns and structures comprised of distinct cell types. However, current methods to model morphogenic events lack control over cell-type co-emergence and offer little capability to selectively perturb specific cell subpopulations. Our in vitro system interrogates cell-cell interactions and multicellular organization within human induced pluripotent stem cell (hiPSC) colonies. We examined effects of induced mosaic knockdown of molecular regulators of cortical tension (ROCK1) and cell-cell adhesion (CDH1) with CRISPR interference. Mosaic knockdown of ROCK1 or CDH1 resulted in differential patterning within hiPSC colonies due to cellular self-organization, while retaining an epithelial pluripotent phenotype. Knockdown induction stimulates a transient wave of differential gene expression within the mixed populations that stabilized in coordination with observed self-organization. Mosaic patterning enables genetic interrogation of emergent multicellular properties, which can facilitate better understanding of the molecular pathways that regulate symmetry-breaking during morphogenesis.

Scientific Abstract:
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